Polymorphisms in the DNA Base Excision Repair Genes *APEX1* and *XRCC1* and Lung Cancer Risk in Xuan Wei, China

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Abstract. *The lung cancer mortality rate in Xuan Wei is among the highest in China and has been causally attributed to high exposure to indoor smoky coal emissions, which contain high levels of PAHs and can lead to modified bases. We studied genetic polymorphisms in four DNA base excision repair genes in a population-based case-control study in Xuan Wei with 122 lung cancer cases and 122 controls. Homozygous carriers of the APEX1 148Glu variant had an increased risk (OR, 2.13; 95% CI, 0.96-4.74), whereas persons with the XRCC1 399Gln allele had a decreased risk (OR, 0.60; 95% CI, 0.35-1.02) of lung cancer compared with wild-type carriers. Subjects with both at-risk genotypes (APEX1 Glu148Glu and XRCC1 Arg399Arg) had a higher risk of lung cancer (OR: 3.34; 95% CI: 1.16-9.67). We found genetic variants in APEX1 and XRCC1 may alter the risk of lung cancer in a special population in China.*

Lung cancer is the leading cause of death from cancer worldwide (1). In rural Xuan Wei County, Yunnan Province, the lung cancer mortality rate is among the highest in China, five times the Chinese national average (2). Unusually, women have similar sex-specific lung cancer mortality rates as men (27.7 and 25.3 per 100,000 for males and females, respectively), even though few women and most men smoked

in Xuan Wei. The wide indoor use of smoky coal without ventilation, which can result in very high levels of polycyclic aromatic hydrocarbon (PAHs), and increased exposure time for women, has been found to be responsible for the high mortality of lung cancer, especially among women (2).

DNA base damage or losses caused by endogenous and exogenous agents occur constantly at a high frequency in human cells. The removal or repair of damaged bases is an important mechanism in protecting the integrity of the genome. Oxidized DNA bases and alkylated DNA bases can be removed and replaced with the correct ones in a localized burst of DNA synthesis by DNA base excision repair pathway, which mobilizes an array of proteins (3). These proteins play an important role in repairing immediate DNA base damage caused by exposure to environmental agents and endogenous reactive oxygen species (ROS) as well as alkylating species (4). Defects in DNA repair can give rise to hypersensitivity to carcinogens and the accumulation of DNA lesions in the genome, and lead to the development of cancer.

A single-nucleotide polymorphism (SNP) is a common genetic variation. Some SNPs may have a functional impact on health outcome and contribute to the overall population risk of cancer. SNPs in DNA repair genes have been suggested to be risk factors for lung cancer but the current available results have been inconsistent (5). We studied the association between genetic variation of DNA base excision repair genes (*APEX1, LIG3, XRCC1* and *ADPRT*) and lung cancer risk for the first time in this unique population.

Materials and Methods

Study design. This was a population-based case-control study of lung cancer in Xuan Wei, China. Details were described elsewhere (6). Briefly, a total of 122 newly diagnosed lung cancer cases and the same number of controls were selected, and individually

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Key Words: Lung cancer, DNA repair, single nucleotide polymorphism, APEX1, XRCC1, ADPRT, LIG3.

Tables I. *Main effect of single nucleotide polymorphisms in DNA base excision repair genes on lung cancer in Xuan Wei.*

Gene SNP (dbSNP ID)	Cases (%) N=119	Controls (%) N=113	OR [a]	95% CI	p value	OR [b]	95% CI	p value
APEX1								
Ex5+5 G>T (rs3136820) *Asp148Glu*								
GG *(Asp/Asp)*	30 (26)	37 (33)	Ref.			Ref.		
GT *(Asp/Glu)*	61 (52)	61 (54)	1.23	0.68-2.25	0.49	1.09	0.59-2.03	0.78
TT *(Glu/Glu)*	26 (22)	15 (13)	2.13	0.96-4.74	0.06	2.01	0.89-4.54	0.09
GT *(Asp/Glu)* + TT *(Glu/Glu)*	87 (74)	76 (67)	1.41	0.80-2.51	0.24	1.28	0.71-2.30	0.41
Trend					0.08			0.12
LIG3								
Ivs18-39 G>A (rs2074522)								
GG	108 (91)	97 (87)	Ref.			Ref.		
GA	11 (9)	14 (13)	0.70	0.30-1.63	0.41	0.66	0.28-1.57	0.35
AA		1 (1)						
GA+AA	11 (9)	15 (13)	0.66	0.29-1.51	0.32	0.62	0.26-1.45	0.27
Ex21-249 C>T (rs1052536)								
CC	60 (51)	56 (50)	Ref.			Ref.		
CT	43 (37)	48 (43)	0.84	0.48-1.46	0.54	0.91	0.52-1.61	0.76
TT	14 (12)	8 (7)	1.64	0.64-4.22	0.30	1.50	0.57-3.96	0.41
CT+TT	57 (49)	56 (50)	0.96	0.57-1.61	0.86	1.00	0.59-1.72	0.98
Trend					0.67			0.66
XRCC1								
Ex10-4 G>A (rs25487) *Arg399Gln*								
GG *(Arg/Arg)*	72 (62)	54 (50)	Ref.			Ref.		
GA *(Arg/Gln)*	40 (34)	51 (47)	0.58	0.34-1.01	0.05	0.56	0.32-0.98	0.04
AA *(Gln/Gln)*	4 (3)	4 (4)	0.76	0.18-3.20	0.71	0.84	0.19-3.67	0.82
GA *(Arg/Gln)* + AA *(Gln/Gln)*	44 (38)	55 (50)	0.60	0.35-1.02	0.06	0.58	0.33-1.00	0.05
Trend					0.09			0.09
Ex9+16 G>A (rs25489) *Arg280His*								
GG *(Arg/Arg)*	76 (68)	81 (74)	Ref.			Ref.		
GA *(Arg/His)*	30 (27)	28 (25)	1.13	0.62-2.08	0.68	1.05	0.57-1.96	0.87
AA *(His/His)*	5 (5)	1 (1)	5.33*	0.57-255.05	0.12			
GA *(Arg/His)* + AA *(His/His)*	35 (32)	29 (26)	1.28	0.72-2.30	0.40	1.20	0.66-2.19	0.54
Ex6-22 C>T (rs1799782) *Arg194Trp*								
CC *(Arg/Arg)*	65 (55)	64 (57)	Ref.			Ref.		
CT *(Arg/Trp)*	41 (35)	40 (36)	1.02	0.58-1.78	0.96	0.93	0.52-1.65	0.80
TT *(Trp/Trp)*	12 (10)	8 (7)	1.49	0.57-3.90	0.42	1.57	0.58-4.21	0.37
CT *(Arg/Trp)* + TT *(Trp/Trp)*	53 (45)	48 (43)	1.09	0.65-1.85	0.74	1.03	0.60-1.77	0.91
Trend					0.54			0.61
ADPRT								
Ex17+8 T>C (rs1136410) *Val762Ala*								
TT *(Val/Val)*	38 (33)	37 (33)	Ref.			Ref.		
TC *(Val/Ala)*	60 (52)	53 (47)	1.12	0.62-2.02	0.71	1.11	0.61-2.03	0.73
CC *(Ala/Ala)*	17 (15)	22 (20)	0.74	0.33-1.60	0.43	0.76	0.33-1.68	0.48
TC *(Val/Ala)* + CC *(Ala/Ala)*	77 (67)	75 (67)	1.00	0.57-1.74	1.00	1.00	0.57-1.77	0.99
Trend					0.57			0.62

[a] Adjusted for age, sex, and current fuel type in unconditional logistic regression.
[b] Adjusted for age, sex, current fuel type, pack-year of smoking, and coal use in unconditional logistic regression.
[c] Fisher's exact estimate and test for the parameter without adjustment for other factors.

Table II. *Stratified analysis of APEX1 Asp148Glu polymorphism by smoking habit among smoking men.*

| | Cases (%) | Controls (%) | OR [a] | 95% CI | *p* value | Cases (%) | Controls (%) | OR [a] | 95% CI | *p* value |
			Male light smokers					Male heavy smokers[c]		
APEX1 (Asp148Glu)										
Asp/Asp	7 (27)	12 (36)	Ref.			9 (22)	12 (38)	Ref.		
Asp/Glu	11 (42)	14 (42)	1.63	0.45-5.94	0.46	21 (51)	18 (56)	1.78	0.57-5.60	0.32
Glu/Glu	8 (31)	7 (21)	2.52	0.57-11.08	0.22	11 (27)	2 (6)	8.85[b]	1.23-116.11	0.02
Asp/Glu + Glu/Glu	19 (73)	21 (64)	1.90	0.57-6.33	0.30	32 (78)	20 (62)	2.50	0.83-7.05	0.10
Trend					0.22					0.02

[a] Adjusted for age and current fuel type in unconditional logistic regression.
[b] exact estimate and test for the parameter with exact logistic regression.
[c] *p* value for multiplicative interaction is 0.36.

Table III. *Joint effect of APEX1 Asp148Glu and XRCC1 Arg399Gln on lung cancer risk.*

APEX1 (Asp148Glu)	*XRCC1 (Arg399Gln)*	Cases	Controls	OR [a]	95% CI	*p* value
Asp/Asp, Asp/Glu	*Arg/Gln, Gln/Gln*	32 (28)	46 (42)			
Asp/Asp, Asp/Glu *Glu/Glu*	*Arg/Arg* *Arg/Gln, Gln/Gln*	68 (60)	57 (52)	1.71	0.96-3.04	0.07
Glu/Glu	*Arg/Arg*	14 (12)	6 (6)	3.34	1.16-9.67	0.04

[a] Adjusted for age and current fuel type in unconditional logistic regression.

matched on sex, age (+/-2 years), village, and type of fuel currently used for cooking and home heating. A standardized structured questionnaire was used to obtain relevant information. For human subject protection, this study was conducted according to the recommendations of the World Medical Association Declaration of Helsinki. The research protocol was approved by a US EPA Human Subjects Research Review Official for international research projects, and informed consent was obtained from all subjects in this study.

Genotyping. DNA was extracted from sputum samples using phenol-chloroform extraction (7) and genotyped by real-time PCR on an ABI 7900HT sequence detection system as described on the SNP500 website (http://snp500cancer.nci.nih.gov) at Core Genotyping Facility of NCI (8). DNA was successfully extracted from 119 cases and 113 controls, and more than 95% of DNA samples were successfully genotyped for all candidate SNPs.

Statistical methods. The Hardy-Weinberg equilibrium for each SNP was tested with the Pearson χ^2 test or exact test (if the cell count was <5). Measures of pairwise linkage disequilibrium (LD) and the identification of haplotype block structure were carried out with HaploView (http://www.broad.mit.edu/personal/jcbarret/ haploview/). Genotype data were analyzed with the homozygote of the common allele as the reference group. Unconditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between lung cancer risk and the SNPs because genotype data were not available for all cases and controls. The main effects of polymorphisms were adjusted for age, sex and

current fuel type in one model, and plus pack-years of smoking and smoky coal use in the other model. Both models gave similar results. The data were also analyzed stratified by sex, smoking habit, and smoky coal use. Individual haplotypes were estimated separately for cases and controls, and overall differences in haplotype frequencies between cases and controls were assessed with the omnibus test using SAS/Genetics (SAS Institute Inc, 2002). Data were analyzed with the Statistical Analysis Software, Version 8.02 (SAS Institute Inc, 1996) if not otherwise specified.

Results

Demographic features were comparable between cases and controls including age, sex, ethnicity, education level, household income, dwelling type, and type of fuel source. The average age for both cases and controls was 55 years and about 35% of the cases and controls were female. About 93% of the males smoked tobacco, while only one female smoked. Compared with studies in other populations, the impact of tobacco smoking in Xuan Wei was not significant (OR: 1.05; 95% CI: 0.32-3.42) using pack-year of smoking as continuous variable, which was consistent with previous studies in Xuan Wei (9). On the other hand, smoky coal use was a more important risk factor in Xuan Wei. Compared with subjects who used less than 130 tons of smoky coal during their lifetime, heavy smoky coal users (> 130 tons) had a 2.27-fold (95% CI = 1.25-4.10) risk of lung cancer.

We genotyped seven SNPs in four genes, which are involved in DNA base excision repair. These polymorphisms included substitutions in both the coding and non-coding regions of the genes. The frequencies of these genotypes among the controls were consistent with Hardy-Weinberg equilibrium (data not shown). The distribution and main effects of these SNPs are shown in Table I, in which the gene name, dbSNP ID, SNP position, base change, and amino acid substitution are also shown. Among these SNPs, homozygous carriers of the *APEX1* variant (*Glu148Glu*) had a borderline significant two-fold risk of lung cancer compared with the homozygotes of the common allele (*Asp148Asp*). Persons carrying *XRCC1 399Gln* variant had a borderline significant 40% decreased risk of lung cancer compared with the wild genotype (*Arg399Arg*). Other SNPs were not associated with lung cancer in this study. When we stratified subjects by sex, we found the impact of the *APEX1 Glu148Glu* genotype was evident only among men. Because most men smoked and only one woman smoked, we further stratified smoking men by pack-years of smoking and found that the effect of the homozygous variant of *APEX1* (*Glu148Glu*) was particularly evident among male heavy smokers with an OR of 8.85 (*p* value=0.02) (Table II). Subgroup analyses showed that age, sex, and lifetime smoky coal use did not modify the effect of other SNPs on lung cancer. In addition, the risk of lung cancer increased along with the increase in number of at-risk alleles from *APEX1* and *XRCC1* (Table III). Subjects with either *APEX1 Glu148Glu* or *XRCC1 Arg399Arg* had an odds ratio of 1.71 (95% CI: 0.96-3.04), and subjects with both of them had an odds ratio of 3.34 (95% CI: 1.16-9.67).

The two SNPs located in *LIG3* and the three SNPs in *XRCC1* were in strong linkage disequilibrium based on measures of pairwise LD, and the SNPs within each gene were found to belong to one haplotype block. The omnibus likelihood ratio tests did not reveal any statistically significant associations with lung cancer (*p*=0.49 for *LIG3*; *p*=0.54 for *XRCC1*).

Discussion

In this population, we found some evidence that the *APEX1 Glu148Glu* genotype and *XRCC1 399Gln* alleles are associated with an altered risk of lung cancer. Endogenous and exogenous exposures can cause damage to DNA bases, which can lead to DNA mutations and strand breaks. PAHs in smoky coal emissions and tobacco can be metabolized *via* an oxidative pathway and produce unstable adducts or reactive oxidative species (10). Our finding of a possible role for base excision repair and risk for lung cancer is consistent with our recent finding that SNPs in other genes that play a role in the generation (*AKR1C3 Gln5His*) or repair (*OGG1 Ser326Cys*) of

oxidative damage may be important in the pathogenesis of lung cancer in this population (10). Adjustment for these SNPs did not change the results presented here, except that the association between lung cancer and *XRCC1 399Gln* (*vs Arg399Arg*) became significant (OR: 0.55; 95% CI: 0.32-0.96; *p*=0.03) with adjustment for *OGG1 Ser326Cys*. Moreover, DeMarini *et al.* previously reported three hot spots for mutations in the *TP53* gene in the lung tumors in Xuan Wei exposed to smoky coal emissions. At least one of the hotspots in the *TP53* mutation spectrum may be due to unstable DNA adducts and/or oxidative damage to the DNA (11). These types of damage can be repaired by base excision repair.

The *APEX1* nuclease is an apurinic/apyrimidinic (AP) endonuclease with 3' phosphatase activities to repair abasic sites. *APEX1* plays a central role in base excision repair of DNA damage (12). The *Asp148Glu* at exon 5 of *APEX1*, a conservative substitution, is positioned at a non-conserved sequence prior to the start of helix No. 4 on the protein surface. It has not been determined if the *148Glu* variant allele has an impact on endonuclease and DNA binding activities (13). However, the *Glu148Glu* genotype has been associated with significantly prolonged cell cycle G2 delays compared with the *Asp148Asp* and *Asp148Glu* genotypes, which suggests that this amino acid substitution may contribute to hypersensitivity to ionizing radiation (14). Our study found that the homozygous variant genotype *APEX1 Glu148Glu* was associated with a significantly increased risk of lung cancer among male heavy smokers. Similarly, a borderline increased risk of *APEX1 Glu148Glu* on lung cancer was found among current smokers in a Japanese population (15). However, this polymorphism was not associated with lung cancer among male smokers in Finland, in which the *Glu148Glu* was the common genotype with a frequency similar to that among lung cancer cases in Xuan Wei (16).

The protein encoded by gene *XRCC1* interacts with DNA ligase III, polymerase beta, and poly (ADP-ribose) polymerase to participate in the base excision repair pathway (3). All three polymorphisms in *XRCC1* occur at amino acid residues that are highly evolutionarily conserved across humans, hamsters, and mice (17). *XRCC1 Arg399Gln* is a non-conservative amino acid substitution within the BRCA1 COOH-terminal side of the poly(ADP-ribose) polymerase binding domain and may affect complex assembly or repair efficiency (18). Current available studies demonstrated that this amino acid change apparently results in either decreased DNA repair capacity or null function by different assays (14,19-24). However, results of epidemiologic studies have been inconsistent so far (16,25-29). Recent research results suggest that the magnitude and direction of the association may depend on the strength of the carcinogenic exposure: the *XRCC1 399Gln* allele had a protective effect against lung cancer for subjects with heavy

exposures, in contrast to an increased risk for people with low exposures (30,31). If it is true that the *399Gln* allele is protective against lung cancer for persons with high exposure to PAHs, it could explain the decreased risk of lung cancer for carriers with the *XRCC1 399Gln* variant that we observed in this study. The local population in Xuan Wei had a particularly high exposure to PAHs due to the wide use of smoky coal for heating and cooking.

In summary, we found that subjects with the *APEX1 Glu148Glu* genotype had an increased risk of lung cancer, especially for heavy smokers, and that the *XRCC1 399Gln* had an inverse association with lung cancer in this population, and that carriers with both at-risk genotypes had a higher risk of lung cancer. The primary limitation of our study is its small sample size and consequently low power, which can lead to both false negative as well as false positive findings and, as such, the findings should be considered preliminary (32). A substantially larger case-control study of lung cancer is being planned in this region and will provide an opportunity to replicate and extend these findings.

Acknowledgements

References

1 Parkin DM, Whelan SL, Ferlay J, Teppo L and Thomas DB: Cancer Incidence in Five Continents. Lyon International Agency for Research on Cancer (IARC) Scientific Publication No. 155, 2002.

2 Mumford JL, He XZ, Chapman RS, Cao SR, Harris DB, Li XM, Xian YL, Jiang WZ, Xu CW, Chuang JC, Wilson WE and Cooke M: Lung cancer and indoor air pollution in Xuan Wei, China. Science *235*: 217-220, 1987.

3 Fortini P, Pascucci B, Parlanti E, D'Errico M, Simonelli V and Dogliotti E: The base excision repair: mechanisms and its relevance for cancer susceptibility. Biochimie *85*: 1053-1071, 2003.

4 Christmann M, Tomicic MT, Roos WP and Kaina B: Mechanisms of human DNA repair: an update. Toxicology *193*: 3-34, 2003.

5 Kiyohara C, Otsu A, Shirakawa T, Fukuda S and Hopkin JM: Genetic polymorphisms and lung cancer susceptibility: a review. Lung Cancer *37*: 241-256, 2002.

6 Lan Q, He X, Costa DJ, Tian L, Rothman N, Hu G and Mumford JL: Indoor coal combustion emissions, GSTM1 and GSTT1 genotypes, and lung cancer risk: a case-control study in Xuan Wei, China. Cancer Epidemiol Biomarkers Prev *9*: 605-608, 2000.

7 Garcia-Closas M, Egan KM, Abruzzo J, Newcomb PA, Titus-Ernstoff L, Franklin T, Bender PK, Beck JC, Le Marchand L, Lum A, Alavanja M, Hayes RB, Rutter J, Buetow K, Brinton LA and Rothman N: Collection of genomic DNA from adults in epidemiological studies by buccal cytobrush and mouthwash. Cancer Epidemiol Biomarkers Prev *10*: 687-696, 2001.

8 Packer BR, Yeager M, Staats B, Welch R, Crenshaw A, Kiley M, Eckert A, Beerman M, Miller E, Bergen A, Rothman N, Strausberg R and Chanock SJ: SNP500Cancer: a public resource for sequence validation and assay development for genetic variation in candidate genes. Nucleic Acids Res *32*: D528-D532, 2004.

9 Lan Q, Chapman RS, Schreinemachers DM, Tian L and He X: Household stove improvement and risk of lung cancer in Xuanwei, China. J Natl Cancer Inst *94*: 826-835, 2002.

10 Lan Q, Mumford JL, Shen M, DeMarini DM, Bonner MR. He X, Yeager M, Welch R, Chanock S, Tian L, Chapman RS, Zheng T, Keohavong P, Caporaso N and Rothman N: Oxidative damage-related genes AKR1C3 and OGG1 modulate risks for lung cancer due to exposure to PAH-rich coal combustion emissions. Carcinogenesis *25*: 2177-2181, 2004.

11 DeMarini DM, Landi S, Tian D, Hanley NM, Li X, Hu F, Roop BC, Mass MJ, Keohavong P, Gao W, Olivier M, Hainaut P and Mumford JL: Lung tumor KRAS and TP53 mutations in nonsmokers reflect exposure to PAH-rich coal combustion emissions. Cancer Res *61*: 6679-6681, 2001.

12 Yoshida A and Ueda T: Human AP endonuclease possesses a significant activity as major 3'-5' exonuclease in human leukemia cells. Biochem Biophys Res Commun *310*: 522-528, 2003.

13 Hadi MZ, Coleman MA, Fidelis K, Mohrenweiser HW and Wilson DM III: Functional characterization of Ape1 variants identified in the human population. Nucleic Acids Res *28*: 3871-3879, 2000.

14 Hu JJ, Smith TR, Miller MS, Mohrenweiser HW, Golden A and Case LD: Amino acid substitution variants of APE1 and XRCC1 genes associated with ionizing radiation sensitivity. Carcinogenesis *22*: 917-922, 2001.

15 Ito H, Matsuo K, Hamajima N, Mitsudomi T, Sugiura T, Saito T, Yasue T, Lee KM, Kang D, Yoo KY, Sato S, Ueda R and Tajima K: Gene-environment interactions between the smoking habit and polymorphisms in the DNA repair genes, APE1 Asp148Glu and XRCC1 Arg399Gln, in Japanese lung cancer risk. Carcinogenesis *25*: 1395-1401, 2004.

16 Misra RR, Ratnasinghe D, Tangrea JA, Virtamo J, Andersen MR, Barrett M, Taylor PR and Albanes D: Polymorphisms in the DNA repair genes XPD, XRCC1, XRCC3, and APE/ref-1, and the risk of lung cancer among male smokers in Finland. Cancer Lett *191*: 171-178, 2003.

17 Lamerdin JE, Montgomery MA, Stilwagen SA, Scheidecker LK, Tebbs RS, Brookman KW, Thompson LH and Carrano AV: Genomic sequence comparison of the human and mouse XRCC1 DNA repair gene regions. Genomics *25*: 547-554, 1995.

18 Masson M, Niedergang C, Schreiber V, Muller S, Menissier-de Murcia J and de Murcia G: XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage. Mol Cell Biol *18*: 3563-3571, 1998.

19 Abdel-Rahman SZ and El Zein RA: The 399Gln polymorphism in the DNA repair gene XRCC1 modulates the genotoxic response induced in human lymphocytes by the tobacco-specific nitrosamine NNK. Cancer Lett *159*: 63-71, 2000.

20 Casse C, Hu YC and Ahrendt SA: The XRCC1 codon 399 Gln allele is associated with adenine to guanine p53 mutations in non-small cell lung cancer. Mutat Res *528*: 19-27, 2003.

21 Gao WM, Romkes M, Day RD, Siegfried JM, Luketich JD, Mady HH, Melhem MF and Keohavong P: Association of the DNA repair gene XPD Asp312Asn polymorphism with p53 gene mutations in tobacco-related non-small cell lung cancer. Carcinogenesis 24: 1671-1676, 2003.

22 Lei YC, Hwang SJ, Chang CC, Kuo HW, Luo JC, Chang MJ and Cheng TJ: Effects on sister chromatid exchange frequency of polymorphisms in DNA repair gene XRCC1 in smokers. Mutat Res 519: 93-101, 2002.

23 Pastorelli R, Cerri A, Mezzetti M, Consonni E and Airoldi L: Effect of DNA repair gene polymorphisms on BPDE-DNA adducts in human lymphocytes. Int J Cancer 100: 9-13, 2002.

24 Lunn RM, Langlois RG, Hsieh LL, Thompson CL and Bell DA: XRCC1 polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. Cancer Res 59: 2557-2561, 1999.

25 Park JY, Lee SY, Jeon HS, Bae NC, Chae SC, Joo S, Kim CH, Park JH, Kam S, Kim IS and Jung TH: Polymorphism of the DNA repair gene XRCC1 and risk of primary lung cancer. Cancer Epidemiol Biomarkers Prev 11: 23-27, 2002.

26 Ratnasinghe D, Yao SX, Tangrea JA, Qiao YL, Andersen MR, Barrett MJ, Giffen CA, Erozan Y, Tockman MS and Taylor PR: Polymorphisms of the DNA repair gene XRCC1 and lung cancer risk. Cancer Epidemiol Biomarkers Prev 10: 119-123, 2001.

27 Butkiewicz D, Rusin M, Enewold L, Shields PG, Chorazy M and Harris CC: Genetic polymorphisms in DNA repair genes and risk of lung cancer. Carcinogenesis 22: 593-597, 2001.

28 Chen S, Tang D, Xue K, Xu L, Ma G, Hsu Y and Cho SS: DNA repair gene XRCC1 and XPD polymorphisms and risk of lung cancer in a Chinese population. Carcinogenesis 23: 1321-1325, 2002.

29 Divine KK, Gilliland FD, Crowell RE, Stidley CA, Bocklage TJ, Cook DL and Belinsky SA: The XRCC1 399 glutamine allele is a risk factor for adenocarcinoma of the lung. Mutat Res 461: 273-278, 2001.

30 Zhou W, Liu G, Miller DP, Thurston SW, Xu LL, Wain JC, Lynch TJ, Su L and Christiani DC: Polymorphisms in the DNA repair genes XRCC1 and ERCC2, smoking, and lung cancer risk. Cancer Epidemiol Biomarkers Prev 12: 359-365, 2003.

31 David-Beabes GL and London SJ: Genetic polymorphism of XRCC1 and lung cancer risk among African-Americans and Caucasians. Lung Cancer 34: 333-339, 2001.

32 Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L and Rothman N: Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst 96: 434-442, 2004.